Pharmacology Biochemistry & Behavior, Vol. 21, pp. 1–3, 1984. © Ankho International Inc. Printed in the U.S.A. 0091-3057/84 $3.00 + .00

Discriminative Stimulus Properties of *S*(−)- and *R*(+)-Cathinone, (+)-Cathine and Several Structural Modifications

RICHARD A. GLENNON,* MARTIN D. SCHECHTER† AND JOHN A. ROSECRANS‡

**Department of Medicinal Chemistry, School of Pharmacy, Medical College of Virginia Virginia Commonwealth University, Richmond, VA 23298*
†Department of Pharmacology, Northeastern Ohio Universities College of Medicine Rootstown, OH 44272
‡Department of Pharmacology and Toxicology, Medical College of Virginia Virginia Commonwealth University, Richmond, VA 23298

Received 12 December 1983

GLENNON, R. A., M. D. SCHECHTER AND J. A. ROSECRANS. *Discriminative stimulus properties of* S(−)- *and* R(+)-*cathinone, (+)-cathine and several structural modifications.* PHARMACOL BIOCHEM BEHAV **21**(1) 1–3, 1984.—Rats trained to discriminate between the stimulus properties of 0.6 mg/kg of racemic cathinone and its vehicle, in a two-lever operant task for food reinforcement, were administered doses of *S*(−)-cathinone, *R*(+)-cathinone, (+)-cathine and several structurally-related derivatives, in order to study structure-activity relationships. The optical isomers of cathinone and (+)-cathine produced patterns of responding similar to that observed with the training drug; *S*(−)-cathinone (ED_{50}=0.22 mg/kg) was the more active of the two isomers, while *R*(+)-cathinone (ED_{50}=0.72 mg/kg) was more active than (+)-cathine (ED_{50}=1.61 mg/kg). In contrast, removal of the α-methyl group of cathinone, or substitution at the 4-position of racemic cathinone by a hydroxyl, methoxyl or chloro group, essentially abolished activity at dose levels comparable to the training dose of cathinone.

Drug discrimination (±)-Cathinone (+)-Cathine Stimulus properties Structure-activity relationships *S*(−)-Cathinone *R*(+)-Cathinone Khat

S(−)-CATHINONE, i.e., 1-phenyl-2-aminopropanone, and (+)-cathine, i.e., (+)-norpseudoephedrine, are two naturally-occurring components of the shrub *Catha edulis* [9,10]. The fresh leaves of this plant (khat) are employed for their central stimulant effect, and it has been suggested that, in humans, repetitive khat-chewing is a form of "psychic dependence" [4]. Both of these agents share a structural resemblance to amphetamine, and cathinone appears to be the active constituent of khat [10]. However, cathine is certainly not without central stimulant properties in man [1]. We recently demonstrated that rats could be trained to discriminate racemic cathinone from vehicle (saline) and that administration of doses of *S*(+)-amphetamine to these cathinone-trained animals resulted in a pattern of responding similar to that produced by the training drug [8]. The purpose of the present study was (a) to evaluate the effects of (+)-cathine in cathinone-trained animals, and (b) to initiate an investigation of structure-activity relationships using several structural modifications of cathinone including its resolved optical isomers.

METHOD

The subjects were eight male ARS/Sprague-Dawley rats weighing between 330–450 g at the beginning of the study. The animals were housed in individual cages, and their weights were maintained at approximately 80–85% of their expected free-feeding weights by partial food deprivation. Water was continuously available in the home cages which were kept in a temperature-controlled (20–22°C) room with a daily cycle of 12 hr (0600–1800) light and 12 hr dark.

The behavioral apparatus consisted of four standard two-lever operant chambers (Lafayette Instruments Corp., Lafayette, IN) housed within individual sound-attenuating cubicles equipped with an exhaust fan and a 9 W house-light. A food pellet receptacle was mounted 2 cm above the grid floor and equidistant between the 2 levers. Solid-state programming equipment (LVB Corp., Lehigh Valley, PA) was used to control and record the sessions and was located in an adjacent room.

The animals used in this study were the same eight rats previously trained to discriminate racemic cathinone from saline; their training has already been described in detail [8]. In brief, these animals were first trained to press one of the levers for food (45 mg Noyes pellets) reinforcement on a fixed ratio 10 (FR 10) schedule. Throughout this training, the animals received daily intraperitoneal (IP) injections of saline 15 min prior to being placed in the operant chamber.

TABLE 1

RESULTS OF GENERALIZATION STUDIES USING ANIMALS TRAINED TO DISCRIMINATE 0.6 mg/kg OF (±)-CATHINONE FROM SALINE

Agent	Dose (mg/kg)	N*	Quantal	Quantitative (±SEM)
(±)-Cathinone	0.6	18	97.9	94.9 (2.3)
Saline (1 ml/kg)		18	2.1	13.7 (1.9)
S(−)-Cathinone	0.15	2	18.8	35.9 (0.9)
	0.30	2	75.0	72.7 (9.9)
	0.45	2	93.8	86.9 (2.4)
R(+)-Cathinone	0.45	2	18.8	31.6 (6.9)
	0.6	2	31.3	37.3 (7.3)
	0.9	2	37.5	48.7 (8.9)
	1.05	2	87.5	81.1 (3.1)
	1.2	2	100	97.6 (0.7)
(+)-Cathine	0.6	2	12.5	29.6 (4.5)
	1.2	2	43.8	46.0 (1.4)
	1.8	2	50.0	52.8 (2.0)
	2.4	2	87.5	83.7 (4.5)
α-Demethylcathinone	0.6	2	0.0	7.1 (0.7)
	1.2	2	6.3	14.8 (3.7)
(±)-4-Hydroxycathinone	0.6	2	0.0	19.8 (0.5)
	1.2	2	6.3	18.0 (4.4)
(±)-4-Methoxycathinone	0.6	2	6.3	18.2 (1.4)
	1.2	2	6.3	21.6 (2.8)
(±)-4-Chlorocathinone	0.6	2	6.3	27.5 (4.0)
	1.2	2	37.5	41.9 (4.7)
	1.8	2	37.5	45.8 (2.9)
	2.4†	1	42.8	48.2

*Number of trials; each trial included all eight animals.

†At this dose, rats exhibited behavioral disruption with delayed responding of between 5–175 min.

The animals were then trained to discriminate 0.6 mg/kg of racemic cathinone administered IP in saline. For half the animals, responding on the left lever was reinforced after administration of drug, while for the other half, responding on the right lever was reinforced following drug administration. Responses on the opposite levers were reinforced after saline administration. Training criterion was reached when the animal selected the appropriate lever, according to the drug (or non-drug) state imposed, on 8 out of ten consecutive sessions.

Generalization Studies

After the rats had attained the discriminative training criterion, sessions of 15 min duration with alternating administrations of 0.6 mg/kg of racemic cathinone and saline were continued on Mondays, Wednesdays and Fridays. This procedure was meant to insure and maintain discrimination to the training drug conditions. On Tuesdays and Thursdays, challenge compounds were administered 15 min before placing the animals in the operant chamber. During these sessions, the animals were allowed to respond in extinction, until 10 responses were made on either lever, and were then returned to their home cages. The lever pressed 10 times first was designated as the "selected" lever. The percentage of rats selecting the lever appropriate for the training drug was the quantal measurement of discrimination. In addition, the total number of responses on both levers, made before 10 responses on either lever were counted, constituted the quantitative measurement, i.e., the number of responses on the "cathinone-correct" lever, divided by total responses made prior to 10 responses, times 100. Where stimulus generalization occurred, the quantal data were analyzed by the method of Litchfield and Wilcoxon [6] which employs probit vs. log-dose effects and generates ED_{50} values.

Drugs

Racemic, *S*(−)- and *R*(+)-cathinone hydrochloride and (+)-cathine hydrochloride were gifts from NIDA via Dr. E. May (MCV/VCU). Racemic 4-methoxycathinone hydrochloride and α-demethylcathinone hydrochloride, i.e., 1-(4-methoxyphenyl)-2-aminopropanone and α-aminoacetophenone, respectively, were available from a previous study [3]. Both of these agents were freshly recrystallized from absolute ethanol prior to their use in this study and their melting points (224–225°C and 190–191°C, d, respectively)

were consistent with those already recorded in the literature [2,5]. The hydrochloride salts of the 4-hydroxy and 4-chloro derivatives of racemic cathinone were prepared according to published literature procedures [2,5]. All agents were dissolved in saline and were administered by IP injection.

RESULTS AND DISCUSSION

The originally-reported [8] cathinone discrimination was maintained throughout the course of this study; the animals consistently responded on the cathinone-appropriate lever when administered 0.6 mg/kg of cathinone, whereas saline administration produced less than 5% of quantal discriminative responses on the same lever (Table 1). Administration of *S*(−)-cathinone, *R*(+)-cathinone and (+)-cathine resulted in a dose-related pattern of responding similar to that observed with the training drug, while α-demethyl-cathinone, racemic 4-hydroxycathinone and 4-methoxycathinone produced saline-like responding at the doses evaluated (Table 1). 4-Chlorocathinone produced saline-like responding at 0.6 mg/kg and partial generalization at doses of 1.2 and 1.8 mg/kg; doses of 2.4 mg/kg produced an initial disruption of behavior (i.e., no responding) that resulted in a 5–175 min delay in responding.

Consistent with the results of other studies on the isomers of cathinone [3,7], *S*(−)-cathinone was found to be more potent than its enantiomer. In the present study, *S*(−)-cathinone (ED_{50}=0.22 mg/kg) is approximately three times more active than *R*(+)-cathinone (ED_{50}=0.72 mg/kg), and is at least as active as (+)-amphetamine (ED_{50}=0.20 mg/kg) and (±)-cathinone (ED_{50}=0.24 mg/kg) in cathinone-trained animals [8]. The α-methyl group of cathinone appears to make a positive contribution to activity, particularly when the absolute configuration about the asymmetric center is *S*, i.e., the same configuration about the chiral center of (+)-amphetamine. The cathinone analog lacking this methyl group, i.e., α-demethylcathinone, is without activity at twice the training dose of the training drug (Table 1). Similar results were obtained when α-demethylcathinone was evaluated as a locomotor stimulant in mice [3].

Cathine is a relatively weak central stimulant in man, being on the order of several-fold less active than amphetamine [1]; in the present study, (+)-cathine (ED_{50}=1.61 mg/kg) produced cathinone-appropriate responding at four times the training dose of cathinone. It has been suggested that aging of khat leaves results in the conversion of cathinone to cathine [10]; thus, it is entirely possible that (+)-cathine may be responsible, at least in part, for some of the central effects produced by the consumption of aged or dried samples of khat.

The metabolism of cathinone has not yet been studied in detail; however, by analogy with amphetamine, it is entirely possible that aromatic hydroxylation might be a potential route of metabolism. For this reason, 4-hydroxycathinone, and two derivatives in which the 4-position of cathinone is blocked, were evaluated. The 4-hydroxy derivative, as well as the 4-methoxy and 4-chloro derivatives, of cathinone failed to produce cathinone-appropriate responding at twice the training dose of cathinone.

In summary, the results of the present study reveal that the naturally-occurring isomer of cathinone, *S*(−)-cathinone, is more active than its *R*(+)-isomer in tests of discriminative control of behavior using animals trained to discriminate 0.6 mg/kg of racemic cathinone from saline. The α-demethyl derivative of cathinone is devoid of cathinone-like activity at twice the training dose of cathinone, while (+)-cathine is approximately 7- to 8-times less active than *S*(−)-cathinone. Substitution at the 4-position of cathinone by a hydroxyl, methoxyl or chloro group essentially abolishes cathinone-like activity at doses comparable to the training dose of cathinone.

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